Acta Clin Croat 2007; 46:41-47 Review

BONE REMODELING AND THYROID FUNCTION

Velimir Altabas, Maja Berković, Branko Bečejac and Miljenko Solter

Department of Endocrinology, Diabetes and Metabolic Diseases, University Department of Medicine, Sestre milosrdnice University Hospital, Zagreb, Croatia

SUMMARY – Many diseases are associated with more rapid bone loss and an increased risk of osteoporosis and fractures. Both hyperthyroidism and hypothyroidism as well as use of thyroid hormones or thyrosuppressant treatment influence bone turnover rates and may alter the risk of future fractures. Markers of bone remodeling are good indicators to determine bone turnover rates and potential bone loss, and correlate well with thyroid hormone levels. Untreated hyperthyroidism accelerates bone turnover resulting in net bone loss, while untreated hypothyroidism in adult humans slows down bone turnover resulting in net bone gain. In both cases, damage in bone microarchitecture occurs, leading to an increased relative risk of fractures. Effective therapies for both states are available, and in ideal case, full recovery of mineralized tissue may occur over time. Controversies are still present in patients receiving suppressive thyroxin treatment for thyroid carcinoma. It seems that suppressed thyroid-stimulating hormone with normal levels of peripheral thyroid hormones may increase the relative fracture risk in postmenopausal but not in premenopausal women. However, the exact molecular mechanisms of thyroid hormone and thyroid-stimulating hormone action on bone are not completely understood yet.

Key words: *Bone remodeling – physiology; Bone and bones – physiology; Bone and bones – metabolism; Thyroid hormones – physiology; Thyroid hormones – deficiency*

Introduction

The skeleton continually undergoes a process of bone remodeling by which old bone is removed and replaced by new bone in two different but coupled processes – bone formation and bone resorption. Bone remodeling in adult humans is thought to have two functions: to provide a means of maintaining normal serum calcium level and to repair microdamage within the skeleton to maintain skeletal integrity and strength[1]. This process can result in one of the following: net gain of bone mass, e.g. during the growth period; constant bone mass in most adult people; and net loss of bone mass, e.g., in osteoporosis.

Net loss of bone is an increasing problem in public health due to aging of the entire population but also due to other risk factors such as smoking, alcohol abuse and chronic diseases[1].

Corresponding address: *Velimir Altabas, MD, MS*, Department of Endocrinology, Diabetes and Metabolic Diseases, University Department of Medicine, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia
E-mail: velimir.altabas@zg.t-com.hr

Received August 24, 2006, accepted in revised form February 5, 2007

Bone Turnover and Bone Mineral Density

Bone formation and bone resorption exist simultaneously in the healthy bone, as a consequence of synchronous and coupled action of osteoblasts and osteoclasts forming remodeling units. The normal bone remodeling cycle lasts for approximately 200 days. During this period, all bone resorbed by osteoclasts should be replaced by new bone produced by osteoblasts. Activation of both cell types is necessary for effective bone remodeling.

The cytokine responsible for communication between the osteoblast (cell responsible for bone formation) and osteoclast (cell responsible for bone resorption) has been identified as a receptor activator of NFkB (RANK) ligand. Osteoprotegerin is a circulating decoy for the RANK receptor. Modulation of osteoclast recruitment and activity appears to be a function of interplay

between these factors[1,2]. Figure 1 shows schematically the mode of osteoclast activation or inactivation.

Although bone resorption and formatting are well balanced processes, imbalance may occur, resulting in net bone loss or net bone gain.

The only way to accurately diagnose changes in bone mass is to measure bone density at at least two points in time. A bone density measurement currently considered the gold standard is dual-energy x-ray absorptiometry (DXA), which allows measurement of any skeletal site as well as the complete skeleton. These results also allow for prediction of the risk of future fractures in patients with osteoporosis.

Markers of bone resorption may help predict the risk of fracture, particularly in older individuals, adding to the predictive value of bone densitometry results. In women 65 years of age or older, when bone density results are equivocal regarding the need of treatment, a high level of bone resorption may be used similarly to a clinical risk factor and suggest the need of treatment even at a higher bone mass level. Another use of biochemical markers is in monitoring response to treatment[1,3].

Several biochemical tests are now available that provide an index of the overall rate of bone remodeling (at a single point in time). Biochemical markers are usually characterized as those related primarily to bone formation (bone-specific alkaline phosphatase, osteocalcin, procollagen type 1 N-terminal propeptide) or bone resorption (urine pyridinoline, urine deoxypyridinoline, serum or urine *N*-telopeptide), as listed in Table 1. Their clinical utility has been limited by high biological and analytical variability within and between individuals[3].

Remodeling rates are regulated by hormones, including estrogens, androgens, thyroid and parathyroid hormones (PTH) as well as vitamin D, cytokines, including numerous growth factors, interleukins (IL 1 and 6), colony-stimulating factors (CSF-1), prostaglandins, tumor necrosis factor α (TNFα), and others[3]. Various modulators of bone remodeling are shown in Table 2.

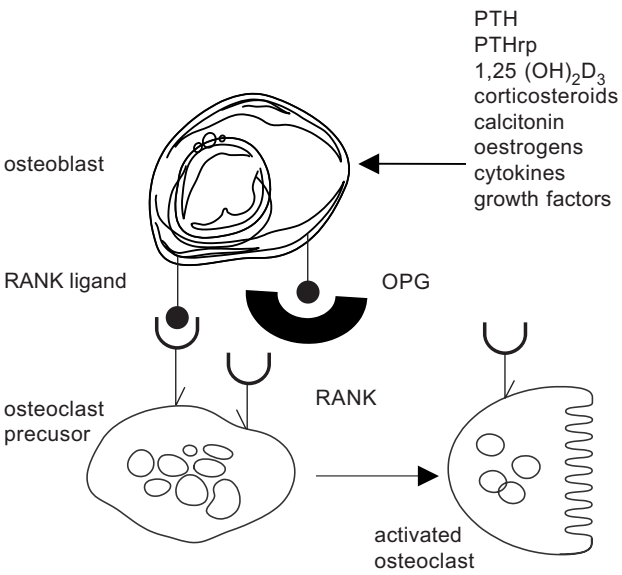

Fig. 1. Osteoblastic control of osteoclast action

Thyroid Hormones and Bone Physiology

Thyroid hormones clearly play a role in normal bone development and bone turnover. The relationship between thyroid hormones and bone was first recognized in the 1890s, when von Recklinghausen reported on a patient with hyperthyroidism and multiple fractures. Over one hundred years later, we know that increased osteoblast and osteoclast activity in hyperthyroidism leads to increased bone turnover, which may result in osteoporosis[4,5]. In contrast, hypothyroidism in adolescents results in delayed skeletal maturation and epiphyseal dysgenesis with long bone growth retardation. In adults, hypothyroidism is associated with reduced bone turnover and osteosclerosis, which is often corrected following thyroid hormone therapy[4,5].

The complex action of thyroid hormone (3,3´,5-triiodothyronine, T3) is mediated by nuclear receptor proteins (TR), which are members of the superfamily of hormone and orphan nuclear receptors and function as hormone-inducible transcription factors. TRs are expressed at sites of intramembranous and endochondral

Table 1. Biochemical markers of bone turnover

Bone formation	Bone resorption
Bone specific alkaline phosphatase (serum)	Hydroxypyridinoline (urine)
Osteocalcin (serum)	Pyridinoline (urine)
Procollagen type 1 N terminal propeptide P1NP (serum)	Deoxypyridinoline (urine)
Procollagen type 1 C terminal propeptide P1CP (serum)	C- and N-telopeptides β-crosslaps (serum, urine)

bone formation in a wide variety of species, including humans. There are several subtypes of TR, expressed in osteoblasts and osteocytes, such as TRα1, TRα2 and TRβ1. TRa1 is a functional receptor that binds T3 and DNA, but TRα2 does not and its physiological role is unknown. TRβ1 seems to have an important role during bone growth in the youth. Perhaps the best evidence for a requirement of T3 is seen in syndromes of thyroid hormone resistance, where a mutation in the gene encoding the β form of the thyroid hormone receptor (TR) often results in abnormal bone development, which may be characterized by short stature, delayed skeletal maturation and abnormal epiphyseal fusion with stipp[6].

Although thyroid hormones directly stimulate bone resorption, it is unlikely that osteoclasts are the primary T3 target cell. Isolated osteoclasts are unable to respond to T3 and require coculture with other bone cells. T3 responses appear to be associated with different patterns of receptor gene expression[6-8].

Osteoprotegerin (OPG) is a newly discovered protein synthesized by osteoblasts, which inhibits osteoclast recruitment, formation and activity. It blocks effects of RANKL (receptor activator nuclear factor – ligand), also produced by osteoblasts, on RANK (receptor activator nuclear factor) which is present on osteoclast surfaces. This pathway seems to be very important in coupling bone formation and resorption[1,2].

T3 stimulates osteoprotegerin synthesis and function, which has an inhibitory effect on osteoclasts[6].

Thyroid hormones accelerate bone remodeling. T3 has been reported to increase the production of osteocalcin, alkaline phosphatase and various cytokines, of which interleukin 6 and 8 should be mentioned, as well as locally acting factors like IGF1 and IGFBP2, resulting in a rise of collagen production and bone protein content. This increase appears to be dose-dependent but high T3 concentration abolishes this effect.

Furthermore, T3 may potentiate some osteoblast responses to PTH by modulating expression of the PTH receptor. Despite many potential T3 target genes identified in osteoblasts, little information is available regarding mechanisms by which their expression is being modulated. Although both osteoblast and osteoclast activities are increased by elevated levels of thyroid hormones, osteoclast activity predominates, resulting in the loss of bone mass.

Osteoclast activation in hyperthyroidism is still poorly understood. Nuclear thyroid receptors were found in osteoclastoma derived osteoclasts, but normal osteoclasts do not express TRα1, excluding the possibility of direct hormonal effects.

However, in hyperthyroid states, osteoclast action exceeds bone formation due to osteoblasts, resulting in bone loss and osteoporosis.

Generally, other cells are needed to promote osteoclast overactivity in hyperthyroidism. Cocultures with osteoblasts have shown paracrine factors of osteoblastic origin such as RANKL and IL-6 to stimulate osteoclast activity.

Some authors believe that osteoclast activation through T3 action seems to be at least in part independent of RANK – RANKL – osteoproteregin interactions.

T3 increased the expression of the osteoprotegerin mRNA, but not of RANKL in unfractionated cultures of bone cells. However, there was a direct stimulatory effect of T3 on cultured mice osteoclast precursor cells,

Table 2. Modulators of bone remodeling

Stimulators		Inhibitors	
Systemically acting factors	Locally acting factors	Systemic hormones	Locally acting factors
Parathyroid hormone	Interleukin 1	Estrogens	Osteoprotegerin
1,25 dihydroxyvitamin D	TNF a	Androgens	Mechanical loading
Parathyroid hormone	Insulin like growth factor	Progesterone	Interferon gamma
related protein	Interleukin 6	Calcitonin	Interleukins 4, 10, 13 and 18
Growth hormone	Prostaglandins	TSH	Transforming growth factor beta
Thyroid hormone	Macrophage colony stimulating factor receptor activator of nuclear factor kappa b ligand (RANK)		

even in the absence of osteoblasts. Added osteoprotegerin did not abolish or diminish this effect. Furthermore, TRa1 was detected in osteoclast precursors suggesting direct T3 action on osteoclast precursor cells. Finally, low levels of TSH allow increased osteoclast formation and survival by augmenting RANK signaling triggered in response to RANK-L[2,7].

TSH and Bone Remodeling

Traditionally, the osteoporosis accompanying human hyperthyroidism that is associated with low TSH levels has been attributed to elevated thyroid hormone (T_3 and T_4) levels. Likewise, the high bone mass accompanying the elevated TSH in hypothyroidism is thought to result from low thyroid hormone levels.

TSH was thought to have only one biologic function, i.e. to regulate the synthesis and secretion of thyroid hormone from thyroid follicular cells. Recently, it has been shown through binding studies and immunodetection that cells and organs other than the thyroid, including lymphocytes, the pituitary, thymus, testes, kidney, brain, adipose tissue, fibroblasts and precursor cells of both osteoblasts and osteoclasts express TSH receptors (TSHR). TSHR is a member of the seven transmembrane G protein-coupled receptor family that also includes the calcitonin and parathyroid hormone receptors, both regulators of bone turnover.

Abe *et al*. demonstrated a direct critical role for TSH in skeletal remodeling that is independent of its effects on circulating thyroid hormone. Using TSHR knockout mice, they found that bone mineral density, in face of normal levels of thyroid hormone, depends on an intact response to TSH. Thus, TSHR null ($TSHR^{-/-}$) mice had low thyroid hormone levels, high TSH levels, severe osteoporosis, and died due to hypothyroidism. TSHR null mice with normal levels of thyroid hormone achieved through hormonal replacement could normalize their body weight, but not their bone density. Even heterozygous $TSHR^{+/-}$ mice with normal levels of thyroid hormone and TSH, but diminished TSH action in bone showed a significant decrease in bone density[9,10].

Interestingly, global osteoporosis was accompanied with focal osteosclerosis in TSHR null mice, indicating that TSH has an effect on both osteoblast and osteoclast function, but independently, without coupling. This phenomenon is undocumented for other molecules so far. Normally, after ovariectomy in mice, or after menopause and during senescence in humans, elevated osteoclastic resorption precedes and exceeds the enhanced bone formation. However, due to the tight coupling between resorption and formation, bone formation also increases, but to a lesser extent than bone resorption. The overall result is osteoporosis, but without focal sclerosis. Formation and resorption are coupled temporally and spatially, so each resorptive cavity was refilled with new bone to maintain skeletal integrity. The main mechanism is osteoclastic activation through the RANK – RANKL – osteoprotegerin pathway and activated osteoblasts. However, it is not clear if activation of this system has a role in the development of hyperthyroidism associated osteoporosis.

TSH seems to exert its effect on osteoblasts and osteoclasts separately *via* TSHR in precursors of both cell types, and osteoclast activation does not depend on RANKL expression in osteoblasts[7].

There is some evidence that TSH directly inhibits TNFα production, leading to suppressed osteoclast formation and action in mice[11].

Hyperthyroidism/Thyrotoxicosis

Thyroid diseases have a high incidence, and their influence on bone homeostasis is often overseen in daily routine. Both hyperthyroidism and hypothyroidism influence bone turnover rates, and may alter the risk of future fractures[4,5].

Increased serum levels of osteocalcin and bone alkaline phosphatase are associated with thyrotoxicosis. Despite increased osteoblast activity, the enhanced bone formation cannot compensate for thyroid hormone-induced increased bone resorption. Increased bone resorption can be detected by using bone resorption markers (e.g., pyridinoline, deoxypyridinoline, β-crosslaps), which are elevated in hyperthyroid patients. Levels of these markers correlate with circulating levels of triiodothyronine[12,13].

Mild hypercalcemia and hypercalciuria can also occur in hyperthyroid patients, but rarely are symptomatic[12].

Increased bone turnover in hyperthyroidism is characterized by an increased number of osteoclasts, resorption sites and ratio of resorptive to formative surfaces. The surface area of unmineralized matrix is also increased.

The bone-remodeling cycle is shortened (from 200 down to 100 days), primarily due to a decreased length

of the formation period, with failure to replace resorbed bone completely. Hystologically, signs of bone porosity occur. Finally, bone mass and bone mineral density are reduced in thyrotoxic patients, leaving these patients with an increased risk of bone fractures[12,14]. There was an increase in the risk of any fracture up to 5 years after a first diagnosis of hyperthyroidism was made, irrespective of the patient's gender or age[12].

Treatment with antithyroid drugs has been associated with a decreased risk of fractures at sites of hip, spine and forearm. There was no dose-response relationship observed between fracture risk and average daily dose of antithyroid drug. It is likely that the antithyroid drugs quickly reverse the increased bone turnover and thereby help restore normal bone mineral content, density and integrity[15]. A surgery for hyperthyroidism decreased the relative risk of fractures at the sites of hip and forearm, with a lesser effect on spine[12].

Hypothyroidism

In most hypothyroid adults, bone density and calcium and phosphate levels are normal, but there is some evidence for reduced bone turnover and prolonged bone – remodeling cycle (up to 700 days). In children, hypothyroidism is associated with delayed linear bone growth and skeletal maturation, in adults with insufficient synthesis of bone matrix proteins (e.g., osteocalcin) and hypermineralization leading to osteosclerosis in extreme cases[4-6]. Data on bone quality and fracture risk in hypothyroid patients are limited, but it seems that even patients with hypothyroidism have an increased risk of fractures, despite higher values of bone mineral density. In patients with untreated hypothyroidism, bone turnover is decreased in both trabecular and cortical bone. Consequently, markers of bone turnover are lower in comparison to euthyroid controls.

However, in addition to the well-known effects of thyroid hormones on bone turnover mediated by the thyroid hormone receptors[16], TSH may also influence bone turnover directly, with high levels of TSH inhibiting bone resorption. This increased risk is probably due to the accumulation of microfractures in bones, which have not been properly repaired[4,15].

As reported in a Danish nationwide follow up study, fracture risk was significantly increased both before and after diagnosis with a peak around the time of diagnosis. An increased risk of fractures in the hip, spine and forearm was seen up to 5 years after the first diagnosis, with a relative fracture risk for the hip site persisting for more than ten years after the first diagnosis. The risk decreased gradually if patients were properly treated with levothyroxine[12].

Little is known about subclinical hypothyroidism, when the levels of thyroid hormones are in the normal laboratory range and only TSH is elevated. In a time-limited placebo controlled study, a group of patients were treated with levothyroxine. A significant increase in bone turnover markers and a decrease in bone mineral density at lumbar spine were demonstrated. The decrease in bone mineral density was interpreted as reactivation of decreased bone remodeling, and not as an iatrogenic bone loss due to levothyroxine. The study period was too short to allow for assumptions towards fracture risk[17].

Controversies are still present in patients receiving suppressive thyroxin treatment for thyroid carcinoma. It seems that suppressed TSH with normal levels of peripheral thyroid hormones may increase the relative fracture risk in postmenopausal but not in premenopausal women[18].

Effects of different thyroid states on bone metabolism are shown in Table 3.

Conclusion

Although the exact mechanisms of thyroid hormone action on bone remodeling are still poorly understood,

Table 3. Effect of different thyroid states on bone metabolism

	Bone resorption	Bone formation	Bone mineral density	Fracture rate
Euthyroidism	⇔	⇔	⇔	⇔
Hyperthyroidism	⇑	⇑	⇓	⇑
Subclinical hyperthyroidism	⇑	⇑	⇓	⇑
Hypothyroidism	⇓	⇓	⇑	⇑

⇔ unchanged; ⇑ elevated; ⇓ decreased

chronic thyrotoxicosis is well recognized as a risk factor for osteoporosis in clinical practice. Thyroid hormone excess increases the activity of both osteoblasts and osteoclasts, resulting in accelerated and increased bone remodeling. The increased osteoclast activity predominates over osteoblast activity, resulting in net loss of cortical and trabecular bone and an increased risk of fractures. Suppressed TSH levels could be an independent contributing factor for osteoporosis, allowing for osteclast overactivity, but data are still conflicting. Hypothyroidism has an effect of decelerated and reduced bone remodeling in adult patients, leading to reduced synthesis of bone matrix proteins and hypermineralization resulting in elevated bone mineral density. However, the risk of future fractures seems to be elevated due to accumulated microfractures. In childhood, hypothyroidism leads to delayed bone maturation. The markers of bone remodeling are good indicators for determining bone turnover rates.

References

1. POGODA P, PRIEMEL M, RUEGER JM, AMLING M. Bone remodeling: new aspects of a key process that controls skeletal maintenance and repair. Osteoporosis Int 2005;16:18-24.
2. BOYLE WJ, SIMONET WS, LACEY DL. Osteoclast differentiation and activation. Nature 2003;432:337-42.
3. SRIVASTAVA AK, VLIET EL, LEWIECKI M, MARICIC M, ABDELMALEK A, GLUCK O. Clinical use of serum and urine bone markers in the management of osteoporosis. Diabetes and Endocrinology [serial online] 2005 [cited 2006 June 5]; 1(1):[6] screens. Available from: URL:http://www.medscape.com/viewarticle/508542?src=search
4. VESTERGAARD P, REJNMARK L, MOSEKLIDE L. Influence of hyper- and hypothyroidism, and the effects of treatment with antithyroid drugs and levothyroxine on fracture risk. Calcif Tissue Int 2005;77:139-44.
5. GREENSPAN S, GREENSPAN FS. The effect of thyroid hormone on skeletal integrity. Ann Intern Med 1999;130:750-8.
6. HARVEY CB, O'SHEA PJ, SCOTT AJ, ROBSON H, SIEBLER T, SHALET SM, *et al*. Molecular mechanism of thyroid hormone effects on bone growth and function. Mol Genet Metab 2002;75:17-30.
7. KANATANI M, SUGIMOTO T, SOWA H, KOBAYASHI T, KANZAWA M, CHIHARA K. Thyroid hormone stimulates osteoclast differentiation by a mechanism independent of RANKL – RANK interaction. J Cell Physiol 2004;201:17-25.
8. BLAIR HC, ZAIDI M. Osteoclastic differentiation and function regulated by old and new pathways. Rev Endocr Metab Disord 2006;7:23-32.
9. ABE E, MARIANS RC, YU W, WU, XB, ANDO T, LI Y, *et al*. TSH is a negative regulator of skeletal remodeling. Cell 2003;115:151-62.
10. SUN L, DAVIES TF BLAIR HC, ABE E, ZAIDI M. TSH and bone loss. Ann N Y Acad Sci 2006;1068:309-18.
11. HASE H, ANDO T, ELDEIRY L, BREBENE A, PENG Y, AMANO H, *et al*. TNFa mediates the skeletal effects of thyroid stimulating hormone. Proc Natl Acad Sci USA 2006;103:12849-54.
12. VESTERGAARD P, MOSEKLID L. Hyperthyroidism, bone mineral, and fracture risk – a meta-analysis. Thyroid 2003;13:585-93.
13. ALTABAS V. Utjecaj tiamazola na koštanu pregradnju u premenopauzalnih žena s hipertireozom. (Influence of thyamazole on bone metabolism in hyperthyroid premenopausal women). PhD dissertation. Zagreb: University of Zagreb, 2005.
14. BAUER DC, ETTINGER B, NEVITT MC, STONE KL. Risk for fracture in women with low serum levels of thyroid-stimulating hormone. Ann Intern Med 2001;134:541-68.
15. MIKOSCH P. Auswirkungen von Schilddruesenfehlfunktionen auf den Knochen. Wien Med Wochenschr 2005;155:444-53.
16. KORŠIĆ M, CVIJETIĆ S, DEKANIĆ-OŽEGOVIĆ D, BOLANČA S, KOZIĆ B. Mineralna gustoća kostiju u bolesnica na dugotrajnoj terapiji levotiroksinom, Lijec Vjesn 1998;120:103-5.
17. MEIER C, MUELLER B, GUGLIELMETTI M, CHRISTCRAIN M, STAUB JJ, KRAENZLIN M. Restoration of euthyroidism accelerates bone turnover in patients with subclinical hypothyroidism: a randomized controlled trial. Osteoporosis Int 2004;15:209-16.
18. QUAN ML, PASIEKA JL, RORSTAD O. Bone mineral density in well-differentiated thyroid cancer patients treated with suppressive thyroxine: a systematic overview of the literature. J Surg Oncol 2002;79:62-70.

Sažetak

KOŠTANA PREGRADNJA I FUNKCIJA ŠTITNJAČE

V. Altabas, M. Berković, B. Bečejac i *M. Solter*

Mnoge bolesti su udružene s ubrzanom koštanom razgradnjom i povećanim rizikom od nastanka osteoporoze. Poremećaji funkcije štitne žlijezde, kao i liječenje hormonima štitnjače, mogu utjecati na brzinu koštane pregradnje te utjecati na rizik od nastanka fraktura. Biljezi koštane pregradnje su dobri pokazatelji za praćenje brzine koštane pregradnje i utvrđivanje rizika od mogućeg gubitka koštane mase, i dobro koreliraju s razinom hormona štitnjače. Neliječena hipertireoza ubrzava koštanu pregradnju dovodeći do gubitka koštane mase, dok neliječena hipotireozaa u ljudi usporava koštanu pregradnju te dovodi do pretjerane mineralizacije skeleta. U oba slučaja dolazi do narušavanja mikroarhitekture i povećanog rizika od nastanka fraktura. Djelotvorna je terapija dostupna za oba poremećaja rada štitne žlijezde i u idealnim će slučajevima dovesti do potpunog oporavka mineraliziranih tkiva. Nesuglasje postoji oko bolesnika koji dobivaju tireosupresivnu terapiju prilikom liječenja karcinoma štitnjače. Izgleda da suprimirane razine TSH i normalne razine perifernih hormona štitnjače mogu povećati relativni rizik za nastanak fraktura u žena nakon menopauze, ali ne i prije nje. Točni molekularni mehanizmi djelovanja hormona štitnjače i TSH na kosti još nisu do kraja rasvijetljeni.

Ključne riječi: *Koštana pregradnja – fiziologija; Kost i kosti – fiziologija; Kost i kosti – metabolizam; Hormoni štitnjače – fiziologija; Hormoni štitnjače - nedostatak*